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ORIGINAL REPORT

Pediatric Melanoma: Risk Factor and Survival Analysis of the Surveillance, Epidemiology and End Results Database

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ABSTRACT

Purpose
To evaluate risk factors for the development of and factors influencing survival in pediatric melanoma.

Patients and Methods
We evaluated 1,255 children (age < 20 years) and 2,673 young adults (age 20 to 24 years) with melanoma in the 2001 National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) database. We estimated exposure to UV radiation based on Environmental Protection Agency (EPA) measurements.

Results
The incidence of pediatric melanoma increased 46% (95% CI, 40 to 52) per year of age and 2.9% (95% CI, 2.1 to 3.6) per year from 1973 to 2001. Incidence rates were lower in black patients (−95%; 95% CI, −98 to −90) compared with white patients and in male patients (−39%; 95% CI −46 to −31) compared with females. Increased ambient UV radiation was associated with elevated risk (19% per kJ; 95% CI, 9 to 30). Children with melanoma had a 5-year melanoma-specific survival of 93.6% (95% CI, 91.9 to 94.9), which improved from 1973 to 2001. The hazard ratio of death from melanoma increased with male sex; older age; advanced disease; location of the primary other than extremities or torso; earlier year of diagnosis; and previous cancer.

Conclusion
The incidence of melanoma in the United States is increasing rapidly in children. Risk factors for pediatric melanoma include being white, being female, increasing age, and environmental UV radiation. Survival is decreased for children and adolescents with unfavorable prognostic factors (male sex, unfavorable site, and/or second primary or regional or distant metastasis). More effective therapeutic strategies are needed for these groups.

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INTRODUCTION

The age-adjusted incidence of malignant melanoma is rapidly increasing in the United States. The rate of increase in all age groups was 2.8% per year from 1981 to 2001 and in children (age < 20 years) was 1.1% per year from 1975 to 2001.[1] The diagnosis is often delayed in children since melanoma is rare (300 to 420 new cases per year), and benign lesions, especially the Spitz nevus, may mimic melanoma.[2,3] The prognosis is good when there is prompt identification and wide local excision of early disease, but poor for those with advanced disease at presentation.[4,5]

Case-control studies in adults have identified multiple host and environmental factors associated with increased risk of malignant melanoma. Host factors include fair skin, white race, blond or red hair, light eye color, tendency to burn with UV radiation

exposure, increased number of benign nevi, dysplastic nevi, family history of melanoma, and xeroderma pigmentosum.[6,7] Environmental factors include sunburns, often as a child, and increased exposure to UV radiation. Proposed risk factors for pediatric melanoma include congenital, dysplastic, or increased number of nevi; inability to tan; blue eyes; facial freckling; family history of melanoma; disorders of DNA excision repair like xeroderma pigmentosum; acquired or congenital immunosuppression; and a previous history of malignancy.[5,8]

Accepted prognostic factors in adult melanoma include primary lesion thickness, ulceration, and nonextremity site; increased age; regional lymph node involvement; satellite or in-transit metastases; elevated serum lactate dehydrogenase level; and visceral or brain metastases.[4,9] However, prognosis and prognostic factors in children are less well defined. In a recent review of more than 300 cases, the outcome for pediatric patients (5-year survival of 74%) was slightly worse than that of young adults, but these survival estimates have limitations.[5] In a large European registry study of children, male sex and lesions on the trunk were associated with a worse prognosis.[10] Advanced stage has been associated with poor prognosis in other pediatric studies.[11,12] The goal of this study was to evaluate risk factors for the development of and factors influencing prognosis in pediatric melanoma.

PATIENTS AND METHODS

Database

The National Cancer Institute Surveillance, Epidemiology and End Results database consists of population-based tumor registries that together include 14% of the population of the United States.[13] Those included in the registries are generally representative of the US population with respect to socioeconomic status and education, but the areas sampled are more urban, with a higher proportion of foreign-born individuals. Most cases (95%) have had continuous follow-up from diagnosis to November 1, 2003, or the time of death. We used SEER*Stat software to access the SEER 12 and the SEER 9 databases; both include data from 1973 to 2001.[14-16]

Case Identification

Selection criteria included diagnosis of malignant melanoma coded according to the International Classification of Childhood Cancer and age less than 25 years.[17] Data extracted on each case included age, sex, year of diagnosis, SEER registry, SEER stage (in situ, localized, regional, or distant), extent of disease including Breslow thickness, ulceration, lymph nodes, and distant metastases, first primary, location of primary, grade, histology, race (white, black, Asian, Native American, or unknown), survival in months, vital status, and cause of death. Thickness, Clark level, and ulceration data were available starting in 1988. Cases were classified as pediatric (age $<$ 20 years) or young adult (age 20 to 24 years) at diagnosis (Table 1).

UV Exposure Estimates

Environmental UV radiation measurements were performed in 1999 and 2000 at the Environmental Protection Agency's (EPA's) network of sites established for this purpose. The EPA provides the daily Diffey-weighted UV irradiance (DUV), the rate at which fair skin will redden, on their Web site (http://www.epa.gov/uvnet/). We calculated the mean of integrated DUV per day over 1 year at the sites within or close to registry areas, after excluding days with poor quality observations per guidelines on the Web site (Table 2).[18] For Connecticut, the mean DUV per day was estimated with a regression model comparing mean DUV to mean UV as measured by Robertson-Berger meters at ground level at weather stations in each registry.[19]

Analysis

Identified cases and associated data were exported to Intercooled Stata 8.2 for Windows (Stata Corp, College Station, TX) for all further analysis.[20] Manual review and exploratory data analysis were used to confirm search criteria. We compared baseline characteristics by the χ^2 test for categoric variables and Student's t test for continuous variables.

We used Intercooled Stata 8.2 to calculate age-adjusted incidence rates and incidence rate ratios (IRR) using the 2000 US census population. Incidence rates and IRR were compared using the χ^2 test.[21] We evaluated the relationship between rates of melanoma and UV radiation, race, sex, age, year of diagnosis, and registry by univariate and multivariate Poisson regression. We used the deviance statistic as a measure of the goodness of fit of the Poisson regression. The significance of indicator variables for race, registry, and adult age was evaluated by the Wald test. The final Poisson model included age, natural log of age, sex, race, UV radiation, and year of diagnosis as independent variables.

We analyzed melanoma-specific mortality using the Kaplan-Meier estimator for the entire group and stratified by variable of interest. We censored cases with other or unknown causes of death (33% of pediatric cases) at the time of death. We compared survival functions with the log-rank test for equality of survival functions. After excluding in situ melanoma, we used a Cox proportional hazards regression model to assess differences in melanoma-specific and all-cause mortality by age group, sex, SEER stage, thickness and location of primary, first primary, histology, and race. We used females with localized melanoma of the extremities and no previous cancer as the reference group. Models were compared with the partial likelihood ratio test. The proportional hazard assumption was examined using time dependent variables. All tests were two-tailed and P values less than .05 were considered significant. The final models included only pediatric cases (age $<$ 20 years).

RESULTS

Case finding using the SEER*Stat program (National Cancer Institute, Bethesda, MD) identified 1,255 cases of melanoma (including 204 in situ cases) in patients younger than 20 years of age and 2,673 cases (including 408 in situ cases) in patients 20 to 24 years old from the 140,206 cases included in the SEER databases from 1973 to 2001. The incidence of melanoma in children (age $<$ 20 years) increased 2.9% (95% CI, 2.1 to 3.6) per year from 1973 to 2001 after

Table 1. Baseline Characteristics of Children and Young Adults With Invasive Melanoma

	Age < 10 Years (n = 95)		Age 10 to 19 Years (n = 956)		Age 20 to 24 Years (n = 2,265)		
	No.	%	No.	%	No.	%	*P*
Extent of disease							< .001
Localized	65	68.4	753	78.8	1,849	81.6	
Regional	14	14.7	89	9.3	198	8.7	
Distant	6	6.3	23	2.4	49	2.2	
Unstaged	10	10.5	91	9.5	169	7.5	
Female	54	56.8	574	60.0	1,441	63.6	.08
Race/ethnicity							< .001
White	81	85.3	876	91.6	2,091	92.3	
Black	4	4.2	4	0.4	10	0.4	
Other	6	6.3	20	2.1	28	1.2	
Unknown	4	4.2	56	5.9	136	6.0	
Previous cancer	6	6.3	16	1.7	45	2.0	< .01
Diagnosis before 1988	40	42.1	393	41.1	1,003	44.3	.25
Histology							< .001
Superficial spreading	10	10.5	345	36.1	989	43.7	
Nodular	9	9.5	61	6.4	168	7.4	
Other	14	14.7	60	6.3	112	4.9	
Not otherwise specified	62	65.3	490	51.2	996	44.0	
Site							< .001
Extremities	35	36.8	397	41.5	970	42.8	
Torso	20	21.1	339	35.5	888	39.2	
Face, head, and neck	28	29.5	154	16.1	248	11.0	
Other	12	12.6	66	6.9	159	7.0	
Thickness, mm							
Mean	3.3*		1.11†		0.94		
SD	0.6		0.07		0.03		
< 1.01	6	6.3	324	33.9	782	34.5	< .001
1.01-2	2	2.1	56	5.9	163	7.2	
2.01-4	7	7.4	47	4.9	65	2.9	
> 4 mm	6	6.3	18	1.9	26	1.2	
Unknown	74	77.9	511	53.5	1,129	54.3	

NOTE. Groups compared by the χ^2 test except for continuous variables.
*$P < .001$ for comparison by two-sided *t* test to adolescents (age 10 to 19 years) or adults (age 20 to 24 years).
†$P < .001$ for comparison by two-sided *t* test to adults (age 20 to 24 years).

adjustment for age, race, sex, and ambient UV radiation in the multivariate Poisson regression. Young adults (age 20 to 24 years) and adolescents (age 10 to 19 years) had similar rates of increase (3.0% per year), while young children (age < 10 years) had a lower rate of increase (1.4% per year). The incidence of melanoma increased with age (46% per year; 95% CI, 40 to 52) and was significantly lower in black patients (−95%; 95% CI, −98 to −90) and Asians and Native Americans (−82%; 95% CI, −88 to −73) compared with white patients (Fig 1). Males had a significantly lower incidence (−39%; 95% CI, −46 to −31) compared with females; primarily due to different rates of melanoma of the extremities (Fig 2). Incidence also varied by registry (ie, residence at the time of diagnosis), but these differences were not significant in the multivariate model. The incidence rate of melanoma was positively correlated with environmental UV radiation (19% per kJ; 95% CI, 9 to 30).

There were significant differences in baseline characteristics of young children (age < 10 years) compared with adolescents and young adults (Table 1). Young children were more likely to be non-white and to have metastases; nodular or other histology; head, face, or neck primaries; thicker lesions; and history of cancer.

Kaplan-Meier estimates of melanoma-specific survival were similar by age group (Fig 3; $P = .20$). Survival significantly decreased with male sex (Fig 4; $P < .005$) or regional or distant metastasis (Fig 5, $P < .001$). Five-year melanoma-specific survival for pediatric cases (age < 20 years) was 100% for in situ disease, 96.1% (95% CI, 94.3 to 97.3) for localized disease, 77.2% (95% CI, 66.4 to 85.0) for regional disease, and 57.3% (95% CI, 33.0 to 75.6) for distant disease. Five-year overall survival was 88.9% (95% CI, 80.3 to 93.9) for young children (age < 10 years), 91.5% (95% CI, 89.5 to 93.1) for adolescents (age 10 to 19 years), and 90.9% (95% CI, 89.6 to 92.0 years) for young adults (age 20 to 24

Table 2. Diffey-Weighted UV Irradiance Levels for Brewer Sites and Distance to Registry

Registry	Brewer Site	Mean Daily DUV (J)	Distance (miles)
Atlanta	Atlanta, GA	2,571	0
Connecticut	Hartford, CT (RB meter)	2,267	0
Detroit	Chicago, IL	2,104	225
Hawaii	Hawaii Volcanoes NP, HI	4,968	0
Iowa	Chicago, IL	2,104	150
New Mexico	Albuquerque, NM	3,660	0
San Francisco/Oakland	Sequoia NP, CA	2,956	100
Seattle	Olympic NP, WA	1,799	50
Utah	Canyonlands NP, UT	3,139	0

Abbreviations: DUV, Diffey-weighted UV irradiance; RB, Robertson-Berger; NP, National Park.

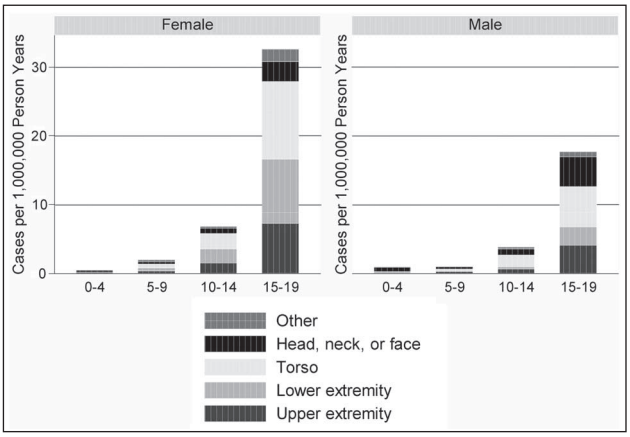

Fig 2. Incidence rates of malignant melanoma in whites stratified by age group, sex, and primary site from the Surveillance, Epidemiology and End Results 9 database (1973 to 2001).

years; $P > .5$) without significant differences by stage (data not shown). After excluding in situ melanoma, 5-year overall survival for pediatric cases (age < 20 years) was 90.9% (95% CI, 88.7 to 92.6).

Univariate Cox proportional hazard analysis showed significantly worse survival for males, patients with regional or unstaged disease; nodular histology; increasing thickness of the primary; primary of the head, face, neck, eye, orbit, CNS, genitals, or overlapping sites; earlier year of diagnosis; and previous cancer (Table 3). The final multivariate model identified similar associations. As information regarding thickness of the primary and nodular histology were not available before 1988, these variables were not included in the final model (Table 3).

DISCUSSION

We analyzed children and young adults with melanoma included in the SEER database between 1973 and 2001. Older age, more recent year of diagnosis, female sex, white race, and increased environmental UV radiation were all associated with a significant increase in the risk of melanoma. Our findings are consistent with earlier analyses of the SEER database,[22,23] and a European population-based study of children.[10] Notably, increasing age confers greater risk in white compared with black individuals. In the first year of life, the incidence of melanoma is similar by race, but it diverges by age 5 to 9 years and is more than 40-fold higher in white individuals by age 20 to 24 years. This results from the logarithmic increase in melanoma incidence in white patients after age 10 years. This pattern may reflect increased susceptibility to UV radiation exposure in white individuals, other environmental factors, and/or differences in genetic predisposition.

The incidence of melanoma is increasing rapidly in children, especially in adolescents. This increase is similar to that seen in young adults. This may reflect increased cumulative UV exposure during childhood or adolescence,

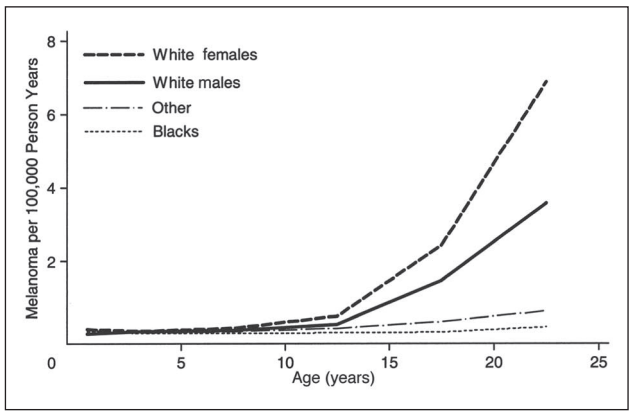

Fig 1. Incidence rates of malignant melanoma in children and young adults stratified by age, sex, and race from the Surveillance, Epidemiology and End Results 9 database (1973 to 2001).

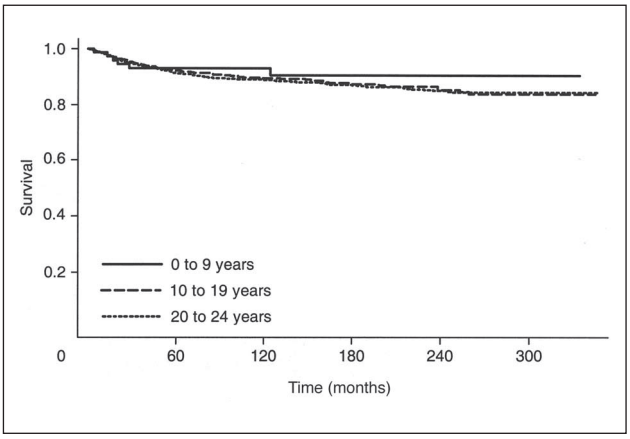

Fig 3. Mortality from malignant melanoma in all races stratified by age group from the Surveillance, Epidemiology and End Results 12 database (1973 to 2001).

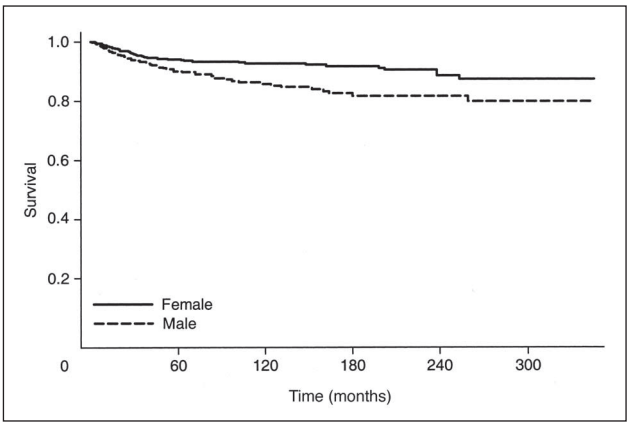

Fig 4. Mortality from malignant melanoma in children (age < 20 years) of all races by sex from the Surveillance, Epidemiology and End Results 12 database (1973 to 2001).

greater awareness and more frequent diagnosis of melanoma (eg, versus atypical Spitz nevus), and/or other environmental factors. Review of the pathology of pediatric melanoma cases in the SEER registries could clarify whether the histologic characteristics have changed over time.

The increased risk of melanoma in girls, particularly on the lower extremities, may be a result of increased UV exposure. In adults, sun-related behaviors differ between men and women.[22] The increased rates of melanoma in adolescent and young women may reflect sunbathing or the widespread (> 25%) practice of indoor tanning.[24]

Increased exposure to UV radiation, measured by number of blistering sunburns (often during childhood), and reported time spent outdoors, confers a two- to five-fold increased risk of melanoma in case-control studies of adults.[23,25-27] Animal models also support the role of early sunburn in the pathogenesis of melanoma.[28] Although case-specific exposure was not directly evaluated in this study, there was a 19% increase in the incidence of melanoma in children per kJ of DUV.

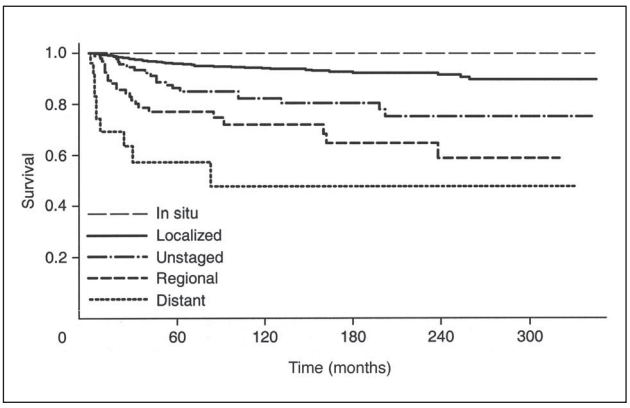

Fig 5. Mortality from malignant melanoma in children (age < 20 years) of all races by extent of disease from the Surveillance, Epidemiology and End Results 12 database (1973 to 2001).

The prognosis for young children, adolescents, and young adults with melanoma appears to be similar. Although the difference in survival was small across age groups in this study, mortality from melanoma in pediatric patients (age < 20 years) increased with older age in the multivariate analysis. Increasing age is a known negative prognostic factor in melanoma of all stages, but this effect is mostly in older adults.[4] We also found increased risk of death in male children, those with regional or distant metastasis, primary sites other than the extremities or torso, increasing thickness of the primary, earlier year of diagnosis, and previous cancer.

Importantly, the thickness of the primary lesion represents one of the strongest prognostic factors in melanoma in adults. This association was evident in children, but the limited numbers of cases with complete data precluded full assessment of its contribution. In the multivariate analysis, other variables (eg, histology, extent of disease) may have accounted for much of the predictive value of thickness. For example, of the 50 patients with primary lesions more than 4 mm in depth and complete staging, 70% had regional or distant disease at presentation.

Melanoma-specific survival in children has improved by approximately 4% per year during the last 3 decades. It is difficult to explain this dramatic improvement. Although earlier diagnosis could be associated with improved survival, there has been no decrease in lesion thickness over the last decade. Furthermore, survival has improved for all stages of pediatric melanoma. The most notable improvement has been in the "unstaged" group, likely due to more complete staging. This group has become smaller over time and there has been a recent increase in the percentage of children with regional disease, which may reflect the increased use of sentinel node biopsy. The application of surgical treatment standards from adults to children with melanoma may have contributed to better local control and improvements in survival. It is unlikely that sentinel lymph node biopsy or systemic therapies have played a significant role because of the limited use of these approaches for pediatric melanoma. However, the prevalence of positive sentinel lymph nodes is higher in patients younger than 35 years than in older adults. This finding supports the recommendation for sentinel lymph node biopsy in adults younger than 35 years and additional indicators of poor prognosis even if their melanoma is less than 1 mm thick.[29] This suggests that sentinel lymph node biopsy should be considered in children with the caveat that the best approach is unknown and requires further investigation.

There are important differences in young children (age < 10 years) with melanoma compared with adolescents and young adults that may reflect distinct tumor biology and/or host characteristics. Younger patients are more likely to

Table 3. Hazard Ratio of Death From Malignant Melanoma in Children Younger Than 20 Years

Variable	Univariate			Multivariate*		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Age (per year)	1.05	0.99 to 1.12	< .15	1.1	1.03 to 1.18	< .005
Male sex	1.8	1.2 to 2.7	< .005	1.6	1.03 to 2.4	< .05
Extent						
Regional	6.1	3.7 to 10	< .001	5.9	3.5 to 10	< .001
Distant†	NA			NA		
Unstaged	3.1	1.8 to 5.3	< .001	2.8	1.6 to 5.0	< .001
Site						
Torso	0.9	0.5 to 1.5	> .5	0.8	0.5 to 1.4	> .5
Face, head, or neck	2.1	1.3 to 3.5	< .005	1.8	1.1 to 3.1	< .05
Other‡	2.6	1.3 to 4.9	< .005	2.7	1.4 to 5.2	< .005
Histology						
Nodular	9.4	4.6 to 19	< .001	NA		
Other	3.1	1.3 to 7.6	< .05	NA		
NOS	3.3	1.8 to 6.1	< .001	NA		
Previous cancer	3.2	1.3 to 7.9	< .05	2.9	1.1 to 7.5	< .05
Year of diagnosis (per year)	0.95	0.93 to 0.98	< .001	0.96	0.94 to 0.99	< .01
Thickness						
1.01 to 2.0 mm	3.2	0.98 to 11	< .1	NA		
2.01 to 4.0 mm	2.9	0.8 to 11	< .15	NA		
> 4.0 mm	18	6.6 to 51	< .001	NA		
Test of trend (per category)	2.4	1.7 to 3.5	< .001	NA		
Unknown	3.6	1.7 to 7.5	< .001			

Abbreviations: NA, not available; NOS, not otherwise specified.
*The multivariate model includes age in years, sex, extent of disease, site, first primary, and year of diagnosis. Baseline hazard was for females with localized malignant melanoma of the extremities and no previous cancer.
†Excluded from results because violated assumption of proportional hazard.
‡Includes melanoma of overlapping regions, genitals, eyes and orbits, mucosa, central nervous system, and NOS.

have congenital nevi and, possibly, syndromes that predispose to cancer. Our data suggest that young children with melanoma are more likely to have poor prognostic features (eg, metastasis, thick primaries, high risk histology, history of cancer). Despite this, survival seems to be similar in adolescents and young adults.

Published large series of pediatric melanoma report 5-year survival rates of 74% to 80%.[5,10] This is significantly worse that the 91% 5-year overall survival seen in our analysis after the exclusion of cases of melanoma in situ. Survival curves calculated from the SEER database are likely to be more accurate for several reasons. Unlike most hospital-based registries and retrospective case series, the SEER database contains many large population-based registries and should be representative of the spectrum of melanoma in the United States. Series from referral centers are likely to be biased by the selection of patients with more advanced disease. On the other hand, although patients with in situ melanoma were excluded from the survival analyses in this study, mortality may still have been underestimated by limiting the analyses to melanoma-specific death. Notably, 33% of the pediatric deaths were not attributable to melanoma, including 10% with missing or uninterpretable death certificates. However, including these deaths did not modify the strength of the associations noted above and only significantly changed survival for regional and distant disease (data not shown). Additionally, those in whom follow-up was incomplete may have been more likely to die. This form of bias may be particularly troublesome in a highly mobile population like that of the US. Fortunately, the SEER database has active follow-up to minimize this cause of information bias. As in all studies, children with melanoma in the SEER database may represent misclassification of benign lesions. The diagnosis of malignant melanoma is particularly challenging in children and concordance of expert dermatopathologists is frequently variable.[30,31] The SEER database, while the standard for population-based cancer registries, has no central review of the diagnostic specimens. There are several additional limitations of these analyses. Incidence rates may have been underestimated in more recent years due to reporting delays. To maximize the inclusion of cases, there is a 2-year delay between the date of diagnosis and inclusion in the SEER database. However, reporting can be delayed for longer than 2 years for diseases, like melanoma, that are frequently diagnosed and treated entirely in the outpatient setting.[32] The environmental measure of UV radiation is an imprecise measure of individual exposure. Information in regard to several putative risk factors for melanoma, including skin type, eye color, family history, number of blistering sunburns, benign

nevi, and acquired or inherited immunodeficiency is not available in the SEER database. Finally, information on histology is frequently incomplete (not specified in 55% of the pediatric cases) and data about thickness, Clark level, and ulceration have only been included since 1988.

In summary, pediatric melanoma is an important and increasing problem. Overall, melanoma in childhood is similar to that in young adults, except that there are greater proportions of cases in males, unusual sites, and thicker primaries. Factors conferring risk of adult melanoma, including older age, white race, environmental exposure to UV radiation, and female sex, are also important in pediatric melanoma. We recommend further study of pediatric melanoma, preferably through the creation of a national cancer registry or use of the existing Rare Tumor Registry of the Children's Oncology Group. With local excision, 5-year survival for pediatric melanoma is excellent, except in the infrequent cases of regional or metastatic disease. For these children, effective systemic therapies are needed and are most likely to be identified through close cooperation of national oncology groups to develop trials that include both children and adults.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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